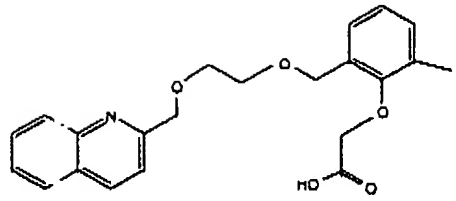
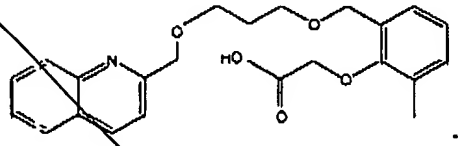
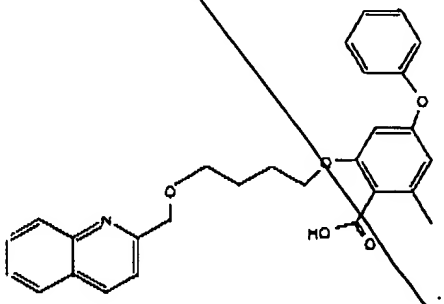


, or



103. (New) A compound the according to claim 1, wherein the compound is



Remarks

I. Correspondence address

The correspondence address for communications relating to this application is as follows:

Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005

The Declaration/Power of Attorney requests that all correspondence be sent to the address above. The Filing Receipt, Notice of Missing Parts and Office Actions of June 6 and August 22, 2001, were mailed to the correct address. The Final Office Action was mailed to an incorrect address.

II. Status of the claims

Claims 1-2, 8, 15, 29-31, 53-59, 61-66, 91-92 and 96-103 are pending in this application. The amendments are intended to remove non-elected subject matter from the claims. The claims now pending should recite the scope of subject matter outlined by the Examiner on page 2 of the Final Office Action. The amendments made to the claims appear in the Appendix.

Applicants amended claims 1 and 2 to confirm that certain recited ring systems are optionally substituted. This was already clear from the definitions of those ring systems in the specification. Claim 29 was amended to delete the definition of Z as a tetrazolyl group. A similar amendment had already been made for claim 1 in the Amendment filed on January 22, 2002. Because a majority of compounds in claims 47-48 constituted non-elected subject matter, applicants canceled those claims in their entirety and added the elected compounds in new claims 102-103.

Claim 54 has been amended to delete reference to "a pharmaceutical salt" of the compound used in the method. The claim recites the use of a compound as claimed in claim 1, which already includes a compound of formula I, a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof. Claim 55 has been amended to refer to the "disorder" recited in claim 54, rather than "disease." This amendment is made as a formal matter to use the same word "disorder" already present in claim 54.

III. Restriction requirement

As indicated above, the pending claims should conform to the restriction requirement made by the Examiner.

The Examiner now states on page 4 of the Final Office Action that not all heterocyclic groups for variable Ar I will be searched. This is not understood. The Restriction Requirement dated June 6, 2001, already divided the claims of this application into twelve groups, allowing applicants to choose Ar I as "non-heterocycle" or "heterocycle" between the groups. The Examiner reaffirmed in the Office Action of August 22, 2001, that the applicants elected Ar I has "heterocycle"

and made the restriction requirement Final. Thus, the first substantive Office Action dated August 22, 2001, presumably would have searched that elected subject matter. Absent a second restriction requirement, applicants decline to amend the claims to a scope less than that elected. If the Examiner makes yet another restriction requirement, applicants respectfully request the examination, at a minimum, of Ar I as a "heteroaryl" as defined in the application.

IV. Rejections under 35 U.S.C. §103(a)

Applicants acknowledge that the Examiner has withdrawn the obviousness rejection over WO 87/05510 to Youssefyeh et al. and U.S. Patent No. 4,794,188 to Musser et al.

V. Rejections under 35 U.S.C. § 112

The Examiner maintained the rejection of many claims under 35 U.S.C. § 112, apparently under the definiteness, written description and enablement requirements. In support of the rejection, the Examiner stated that the claims do not tell the reader what is claimed. The Examiner also stated that many of the compounds have not been made yet, and the Examiner questioned the starting materials for the synthesis of the compounds. The Examiner also stated that applicants are required to demonstrate that all the compounds claimed possess the disclosed utility. Applicants respectfully traverse this rejection.

The boundaries of the claims are sufficiently clear to inform the public what is claimed. For example, claim 1 presents a structural formula I with different variables. The specification devotes at least nine pages (pages 7-16) to explain the definitions of words used in the claims The scope of the claims can be determined in a methodical analysis of the variables recited in the claims and their given definitions. The reader of the claims does not become a co-inventor simply by reading the claims.

This application recites a number of example compounds and many example syntheses demonstrating the making of those compounds. The requirements of 35 U.S.C. § 112 do not require applicants to make every compound falling within the

scope of the claims. The specification at pages 54-71 provides ample description of how to make the compounds, including detailed reaction schemes. The Examples from pages 75-118 furthermore illustrate the making of a large number of specific compounds. With regard to the utility of the claimed compounds, the specification makes clear that the compounds of claim 1 have utility for one or more purposes described on pages 17-20. Lastly, the Examiner commented that applicants are expected, in return for the patent grant for 17/20 years, "a specific fact disclosure." Applicants agree that certain requirements present in, for example, section 112 of the patent statute, relate to the sufficiency of a patent specification. The present disclosure satisfies all applicable disclosure requirements.

VI. Rejection under 35 U.S.C. § 112, first paragraph

The Examiner maintained the rejection of the method of use claims under 35 U.S.C. § 112, first paragraph, as non-enabled. Applicants respectfully traverse the rejection.

The Examiner stated that the claims were not enabled for treatments capable of being modulated by the compounds having agonistic as well as antagonistic activity. To the extent that this rejection relates to original claims 67-68, which recite the mediation as agonistic or antagonistic, the rejection should be withdrawn because applicants have canceled those claims.

The present disclosure provides a credible basis to support the treatments recited in the pending claims. The treatment in claim 54, of a disorder capable of being modulated by a compound having PPAR ligand binding activity, appears credible on its face, especially in light of the activity of the claimed compounds as PPAR ligand receptor binders.

As stated in the specification, compounds having PPAR ligand binding activity can be used, for example, in cell differentiation that produces lipid accumulating cells, and in the regulation of insulin sensitivity and blood glucose levels. Page 18, lines 9-11. Thus, the method of claim 55, which involves treating a disorder associated with detrimental levels of insulin, glucose, free fatty acids or triglycerides, also appears credible in light of the activity of the claimed compounds. Furthermore,

C

given the underlying roles of insulin sensitivity and blood glucose levels in the hyperglycemia and hyperinsulinemia, it logically follows that the ability of the claimed compounds to regulate insulin sensitivity and blood glucose levels renders them candidates for the treatment of hyperglycemia (including diabetes and Type II diabetes), hyperinsulinemia and insulin resistance as recited in claims 56-59 and 61.

The specification at page 18, lines 14-15, indicates that the physiological disorders of macrophage differentiation, which leads to the formation of atherosclerotic plaques, can be modulated by compounds having PPAR ligand binding activity. Thus, the specification sets forth a credible basis for use of the claimed compounds, as PPAR ligand binders, in the treatment of cardiovascular conditions such as atherosclerosis as claimed in claims 62-63.

For claim 64, use of the compounds in the treatment of hyperlipidemia logically follows from the disclosed effect of the compounds on cell differentiation and its production of lipid accumulating cells. Page 18, lines 10-11. Also as explained in the specification, obesity is an excessive accumulation of adipose tissue, and PPARγ is believed to play a central role in adipocyte gene expression and differentiation. Page 1, lines 23-24. Excess adipose tissue is associated with the development of serious medical conditions, for example, hypertension and hyperlipidemia obesity. Page 1, lines 26-27. Thus, a credible basis exists to believe that the compounds of the invention are useful in the treatment of hypertension and eating disorders as claimed in claims 65-66.

In light of the above, the present claim language satisfies the definiteness requirement, the specification adequately instructs those skilled in the art how to practice the invention, and the invention is patentable over the art. If there is any fee due in connection with the filing of this Amendment, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

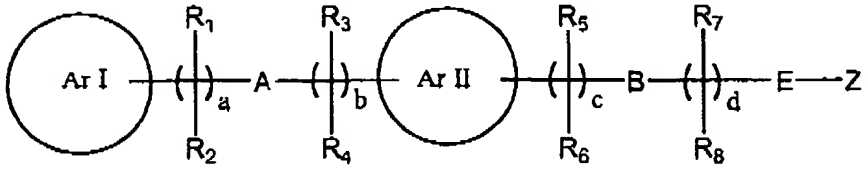
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

By: _____
Steven J. Scott
Reg. No. 43,911

Date: June 5, 2002

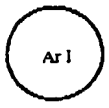
Appendix Detailing Amendments to Application

1. (Three Times Amended) A compound of formula (I)



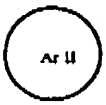
(I)

wherein:



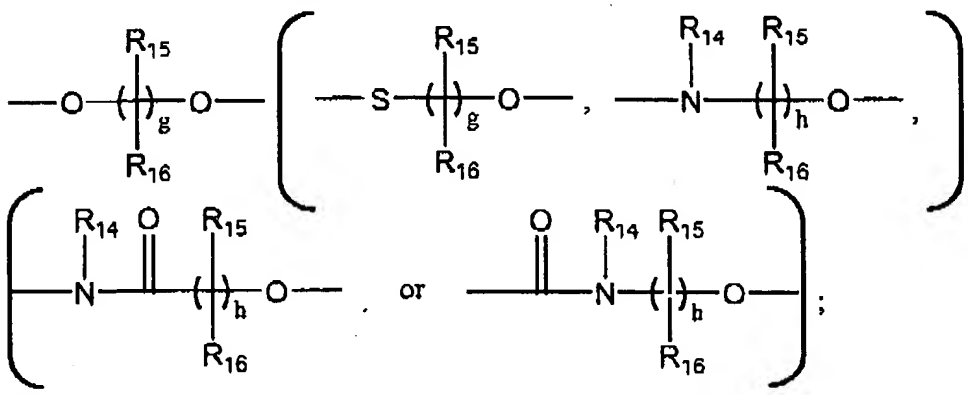
is [and 

are independently aryl, fused arylcycloalkenyl, fused arylcycloalkyl,] fused arylheterocyclenyl, fused arylheterocyclyl, heteroaryl, fused heteroarylcycloalkenyl, fused heteroarylcycloalkyl, fused heteroarylheterocyclenyl, or fused heteroarylheterocyclyl, all of which are optionally substituted;



is optionally substituted phenyl;

A is [-O-, -S-, -SO-, -SO_2-, -NR_{13}-, -C(O)-, -$N(R_{14})C(O)$-, -$C(O)N(R_{15})$-, -$N(R_{14})C(O)N(R_{15})$-, -$C(R_{14})$=N-, a chemical bond,]



B and E are a chemical bond;

a is 0-6;

b is 0-4;

c is 0;

d is 0;

g is 1-5;

[h is 1-4;]

R_1, R_2, R_3 and R_4 are, independently, hydrogen, halogen or alkyl;

[R_1, R_3, R_5 and R_7, are independently hydrogen, halogen, alkyl, carboxyl, alkoxycarbonyl or aralkyl;

R_2, R_4, R_6 and R_8, are independently $-(CH_2)_q-X$;

q is 0-3;

X is hydrogen, halogen, alkyl, alkenyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, alkoxy, aralkoxy, heteroaralkoxy, carboxyl, alkoxycarbonyl, tetrazolyl, acyl, acylHNSO$_2$-, -SR$_{23}$, Y^1Y^2N- or Y^3Y^4NCO-;

Y^1 and Y^2 are independently hydrogen, alkyl, aryl, aralkyl or heteroaralkyl, or one of Y^1 and Y^2 is hydrogen or alkyl and the other of Y^1 and Y^2 is acyl or aroyl;

Y^3 and Y^4 are independently hydrogen, alkyl, aryl, aralkyl or heteroaralkyl;]

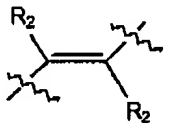
Z is $R_{21}O_2C$-, $R_{21}OC$-, [cyclo-imide,] -CN, $R_{21}O_2SHNCO$-, $R_{21}O_2SHN$-, $(R_{21})_2NCO$- [,] or $R_{21}O$- [, or 2,4-thiazolidinedionyl]; and

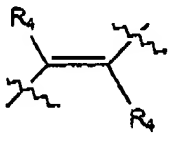
R_{21} is independently hydrogen, alkyl, aryl, cycloalkyl, or aralkyl;

[R_{13} and R_{23} are independently $R_{22}OC$-, $R_{22}NHOC$-, hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, heteroaralkyl, or aralkyl];

[R_{14},] R_{15}, R_{16} are independently hydrogen, alkyl, aralkyl, carbonyl, or alkoxycarbonyl;

[or R_{14}, and R_{15} taken together with the carbon and nitrogen atoms through which they are linked form a 5 or 6-membered azaheterocyclyl group; or

when a is 2-6, then at least one pair of vicinal R_1 radicals taken together with the carbon atoms to which the R_1 radicals are linked form a  group; or

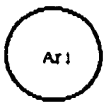
when b is 2-4, then at least one pair of vicinal R_3 radicals taken together with the carbon atoms to which the R_3 radicals are linked form a  group; or

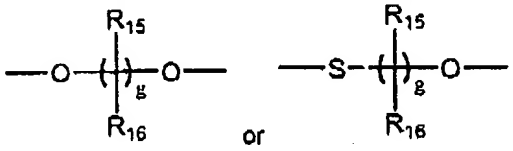
geminal R_5 and R_6 radicals taken together with the carbon atom through which these radicals are linked form a 5 membered cycloalkyl group; or

geminal R_7 and R_8 radicals taken together with the carbon atom through which these radicals are linked form a 5 membered cycloalkyl group; and

R_{22} is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, heteroaralkyl, or aralkyl;] or

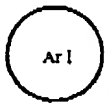
a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

2. (Amended) A compound according to claim 1 wherein  is [optionally substituted aryl,] optionally substituted azaheteroaryl, or optionally substituted fused arylheterocyclenyl or optionally substituted fused arylheterocyclyl [; and  is optionally substituted phenyl or optionally substituted naphthyl, optionally substituted heteroaryl, or optionally substituted fused arylheterocyclenyl].

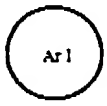
8. (Amended) A compound according to claim 1 wherein a = 0; [A is  or ;] R_{15} and R_{16} are hydrogen; g is 1, 2, 3 or 4; and b = 0.

15. (Amended) A compound according to claim 1 wherein [c = 0; d = 0; B and E is a chemical bond;] Z is $R_{21}O_2SHNCO$-, and R_{21} is phenyl.

29. (Amended) A compound according to claim 1 wherein Z is $-CO_2H$ [,] or -CN [or a tetrazolyl group].

30. (Twice Amended) A compound according to claim 1 wherein 

is an optionally substituted quinolinyl, quinoxalinyl, quinazolinyl, isoquinolinyl, *N*-alkyl-quinolin-4-onyl, quinazolin-4-onyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzofuranyl, benzothiophenyl, indolinyl oxazolyl, thiazolyl, oxadiazolyl isoxazolyl, imidazolyl, pyrazol-yl, thiadiazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl [,] or pyridazinyl [, phenyl, or napthalenyl] group, wherein the substituent is a ring system substituent.

31. (Twice Amended) A compound according to claim 1 wherein 

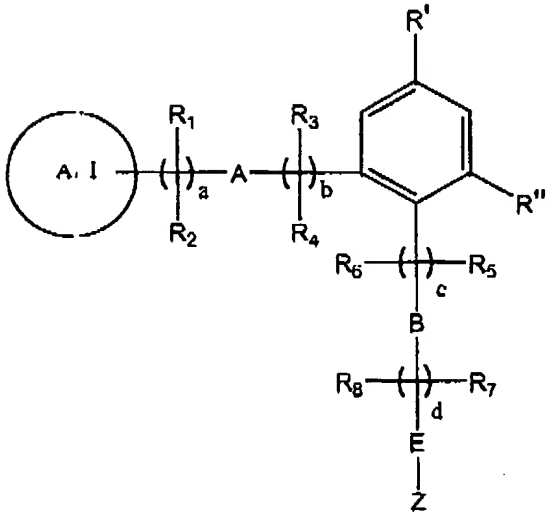
is unsubstituted quinolin-2-yl, 3-substituted quinolin-2-yl, 4-substituted quinolin-2-yl, 6-substituted quinolin-2-yl or 7 substituted quinolin-2-yl; an unsubstituted quinozalin-2-yl, 3-substituted quinozalin-2-yl, 6-substituted quinozalin-2-yl or 3,6-disubstituted quinozalin-2-yl; unsubstituted quinazolin-2-yl, 4-substituted quinazolin-2-yl or 6-substituted quinazolin-2-yl; unsubstituted isoquinolin-3-yl, 6-substituted isoquinolin-3-yl or 7-substituted isoquinolin-3-yl; 3-substituted-quinazolin-4-on-2-yl; *N*-substituted quinolin-4-on-2-yl; 2-substituted-oxazol-4-yl or 2,5 disubstituted-oxazol-4-yl; 4-substituted oxazol-2-yl or 4,5-disubstituted-oxazol-2-yl; 2-substituted thiazol-4-yl or 2,5-disubstituted thiazol-4-yl; 4-substituted thiazol-2-yl or 4,5-disubstituted-thiazol-2-yl; 5-substituted-[1,2,4]oxadiazol-3-yl; 3-substituted-[1,2,4] oxadiazol-5-yl; 5-substituted-imidazol-2-yl or 3,5-disubstituted-imidazol-2-yl; 2-substituted-imidazol-5-yl or 2,3-disubstituted-imidazol-5-yl; 3-substituted-isoxazol-5-yl; 5-substituted-isoxazol-3-yl; 5-substituted-[1,2,4] thiadiazol-3-yl; 3-substituted-[1,2,4]-thiadiazol-5-yl; 2-substituted-[1,3,4]-thiadiazol-5-yl; 2-substituted-[1,3,4]-oxadiazol-5-yl; 1-substituted-pyrazol-3-yl; 3-substituted-pyrazol-5-yl; 3-substituted-[1,2,4]-triazol-5-yl; 1-substituted-[1,2,4]-triazol-3-yl; 3-substituted pyridin-2-yl, 5-substituted pyridin-2-yl,

6-substituted pyridin-2-yl or 3,5-disubstituted pyridin-2-yl; 3-substituted pyrazin-2-yl, 5-substituted pyrazin-2-yl, 6-substituted pyrazin-2-yl or 3,5 disubstituted-pyrazin-2-yl; 5-substituted pyrimidin-2-yl or 6-substituted-pyrimidin-2-yl; 6-substituted-pyridazin-3-yl or 4,6-disubstituted-pyridazin-3-yl; [unsubstituted napthalen-2-yl, 3-substituted napthalen-2-yl, 4-substituted napthalen-2-yl, 6-substituted napthalen-2-yl or 7 substituted napthalen-2-yl; 2-substituted phenyl, 4-substituted phenyl or 2,4-disubstituted phenyl;] unsubstituted -benzothiazol-2-yl or 5-substituted-benzothiazol-2-yl; unsubstituted benzoxazol-2yl or 5-substituted-benzoxazol-2yl; unsubstituted -benzimidazol-2-yl or 5-substituted-benzimidazol-2-yl; unsubstituted -thiophen-2yl, 3-substituted -thiophen-2yl, 6-substituted -thiophen-2yl or 3,6-disubstituted-thiophen-2yl; unsubstituted -benzofuran-2-y, 3-substituted-benzofuran-2-yl, 6-substituted-benzofuran-2-yl or 3,6-disubstituted-benzofuran-2-yl; 3-substituted-benzofuran-6-yl or 3,7-disubstituted-benzofuran-6-yl, wherein the substituent is a ring system substituent.

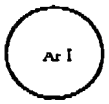
54. (Amended) A method of treating a patient suffering from a physiological disorder capable of being modulated by a compound according to claim 1 having PPAR ligand binding activity, comprising administering to the patient a pharmaceutically effective amount of the compound [, or a pharmaceutically acceptable salt thereof].

55. (Twice Amended) A method according to claim 54 wherein the <u>disorder</u> [disease] is associated with a physiological detrimental blood level of insulin, glucose, free fatty acids, or triglycerides.

97. (Amended) A compound as claimed in claim 1, which is of formula



wherein

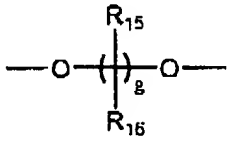


is optionally substituted heteroaryl;

a = 1;

b = 0;

R_1, R_2, R_3, R_4 are hydrogen



A is ;

[R_5, R_6, R_7, R_8,] R_{15}, R_{16} are hydrogen;

c = 0;

d = 0;

g = 2, 3, 4 or 5;

B and E are a chemical bond;

Z is $R_{21}O_2C$-, $R_{21}OC$-, or $R_{21}O$-;

R_{21} is hydrogen, alkyl, aryl, cycloalkyl, or aralkyl;

R' is hydrogen, lower alkyl, halo, alkoxy, aryloxy or aralkyloxy; and

R" is lower alkyl, hydrogen, aralkyloxy, alkoxy, cycloalkylalkyloxy or halo, or

a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

C